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(54) Title: TWO NOVEL cAMP-SPECIFIC PHOSPHODIESTERASE (PDE4B) ISOFORMS AND RELATED TECHNOLOGY

(57) **Abstract:** Two novel cAMP-specific isoforms of rat PDE4B are disclosed. pRPDE90 is a cDNA encoding a 659-amino acid-long protein with a large region corresponding to similar regions found in PDE4B1 and PDE4B3. It is separated from these isoforms by a 17-amino acid region found at its extreme amino-terminal end which shows no homology to any previously-cloned sequence. pRPDE89 is a rat cDNA which encodes a 726-amino acid-long protein which is 96 % identical to the human PDE4B1 phosphodiesterase isoform.

TWO NOVEL cAMP-SPECIFIC PHOSPHODIESTERASE (PDE4B) ISOFORMS AND RELATED TECHNOLOGY

1. Related Applications

This application is related to and claims the benefit of United States Provisional Application Serial No. 60/170,562 of Graeme B. Bolger, filed December 14, 1999 and entitled "Two Novel cAMP-Specific Phosphodiesterase (PDE4B) Isoforms and Related Technology," which is incorporated herein by reference.

2. Field of the Invention

The present invention relates to cyclic AMP-specific phosphodiesterases (PDE4 enzymes), which help regulate physiological processes by hydrolizing cAMP, an intracellular signaling molecule. Specifically, the invention relates to two novel cAMP-specific phosphodiesterase isoforms which are expressed in many body tissues, including the brain.

3. Technical Background

Cyclic AMP ("cAMP") is an intracellular signaling molecule involved in many important cellular processes. Specifically, cAMP is critical to signaling pathways which regulate physiological processes such as those involved in vascular smooth muscle, the immune system, and the brain. cAMP-specific phosphodiesterases, referred to as "PDE4 enzymes," hydrolyze cAMP and thus regulate these pathways in cells. The cAMP-specific phosphodiesterases can be differentiated from other cyclic nucleotide phosphodiesterase ("PDE") families by sequence homology in the catalytic region of the proteins as well as by their ability to be inhibited by a specific class of drugs, such as rolipram. Beavo, *Physiol. Rev.* 75:725–48 (1995). Rolipram and other specific PDE4 inhibitors have anti-depressant, anti-inflammatory and smooth muscle relaxant properties in humans. Houslay et al., *Advances in Pharmacology,* 44:225–342 (1998). PDE4 enzymes are also characterized by the presence of unique "signature" regions of sequence, called <u>u</u>pstream <u>c</u>onserved <u>r</u>egions, or "UCR," such as UCR1 and UCR2, which are located in the amino-terminal third of the proteins. Houslay, et al., *supra;* Bolger et al., *Mol. Cell Biol.,* 13:6558–71 (1993).

PDE4 enzymes are also the closest vertebrate homologs of the *dunce* gene of *Drosophila melanogaster*, which was isolated as a mutation affecting learning and memory. Davis, *Physiol. Rev.* 76:299–317 (1996). The mammalian PDE4s are encoded by four genes (*PDE4A*, *PDE4B*, *PDE4C* and *PDE4D*), and it has been shown by several researchers that additional diversity in this family is produced by alternative mRNA splicing. Bolger et al., *supra*; Sette et al., *J. Biol. Chem.*, 269(32):20806 (Aug. 12, 1994); Bolger et al., *J. Biol. Chem.*, 271:1065–71 (1996); Bolger et al., *Biochem. J.*, 328:539–48 (1997); Naro et al., *Endocrinology*, 137:2464–72 (1996); Huston et al., *Biochem J.* 328:549–56 (1997). See Houslay et al., *supra*, for a review of these findings. Often the alternatively-spliced isoforms have different tissue expression patterns, a fact which suggests that each may have a distinct function.

Intracellular signaling molecules are important since they transmit a signal received outside of the cell to target molecules in the cytosol, thus allowing a cell to react to changes in its environment. This transmission is generally a multistep process often having at least the general steps laid out in the following cAMP-specific sequence: First, an extracellular ligand binds to a plasma membrane-bound receptor molecule which has a binding domain extending into the extracellular space and a domain extending into the cytosol. Second, the binding of the ligand to the extracellular domain changes the conformation of the cytosolic domain, thus causing it to bind to a G-protein. Third, the G-protein, in turn, activates a plasma membrane enzyme which produces cAMP (adenylyl cyclase). Fourth, the cAMP then binds to target molecules in the cytosol, thus altering their conformation and activity. Finally, cyclic AMP-specific phosphodiesterases rapidly break down the cAMP, hydrolizing it to form adenosine 5'-monophosphate.

As seen in the final step, in order to use cAMP as a signaling molecule, a cell must be able to quickly manipulate the levels of cAMP present in response to signals transmitted to the outside of the cell. Cyclic AMP functions well in this respect, having been shown in some cases to respond to hormonal stimulation by increasing in cellular concentration by five-fold within seconds.

Such rapid changes in cAMP levels are possible due to a cell's ability to rapidly synthesize cAMP. Cells are also adapted to rapidly break down cAMP. Cyclic AMP is synthesized from ATP by adenylyl cyclase, an enzyme found in the plasma membrane of a cell. Cyclic AMP is hydrolized by cyclic AMP phosphodiesterases to form adenosine

5'-monophosphate ("5'-AMP"). These phosphodiesterases are found in many tissues, including specific regions of the brain.

It is known that certain cAMP-specific phosphodiesterases ("PDE4 enzymes") are the targets of inhibitors. Some of these inhibitors have been shown to have positive effects on the brain, including exhibiting anti-depressant properties, memory-enhancing qualities, and other positive effects on the function of the central nervous system. Unfortunately, however, these beneficial effects are often accompanied by nausea and other gastrointestinal side effects. These negative side effects are likely mediated at least in part by the action of the inhibitors used on the brain. The number of isoforms of the PDE4 enzymes present in the brain is currently unknown, as is an understanding of which inhibitors affect which phosphodiesterases. Knowledge of novel isoforms of PDE4 enzymes would be a great advancement in the art, allowing researchers and health professionals to learn to target PDE4 inhibitors to specific isoforms and limit the effects of the inhibition to the desired, positive effects, while avoiding inhibition of those isoforms whose inhibition causes the deleterious side effects noted above.

From the foregoing, it will be appreciated that it would be an advancement in the art to identify additional PDE4 enzyme isoforms. Such identification would enable investigation of the patterns of isoform tissue expression, and thus allow selective targeting of specific isoforms with isoform-specific inhibitors, yielding effective use of the beneficial effects of inhibition while avoiding the deleterious ones.

Such novel PDE4 enzyme isoforms are disclosed herein.

4. **Brief Summary of the Invention:**

The present invention relates to isoforms of cAMP-specific phosphodiesterase. Specifically, two rat cDNAs, pRPDE89 and pRPDE90, were isolated from a rat cerebral cortex cDNA library. Both of these were found to encode novel PDE4B isoforms. The invention thus comprises a first cDNA, pRPDE89, which encodes a protein identical in length to that encoded by the previously-described human PDE4B1 isoform known in the art. The protein encoded by both the rat and human genetic material is 736 amino acids in length. This rat cAMP-specific phosphodiesterase isoform is over 96% identical in sequence to the human PDE4B1 isoform.

The invention further comprises a second cDNA, pRPDE90, which encodes a

novel protein of 659 amino acids, called PDE4B4. PDE4B4 has a novel N-terminal region of 17 amino acids which is not present in any other known PDE4B isoform. The remaining 642 amino acids of PDE4B4 are identical to those found in corresponding regions of the PDE4B1 and PDE4B3 isoforms. Without being bound to any particular theory, it is believed that the structures of the cDNAs encoding the PDE4B1, PDE4B3, and PDE4B4 isoforms are generated by alternative mRNA splicing and through the use of alternative promoters of the *PDE4B* gene. RNase protection and immunoblotting demonstrated the presence of mRNA and protein specific for each of the PDE4B1, PDE4B2, PDE4B3 and PDE4B4 isoforms, respectively, in a wide range of tissues, including various regions of the brain.

Since various inhibitors of cAMP phosphodiesterases have been shown to have anti-depressant and memory enhancement effects, the discovery of novel isoforms of PDE4B opens possibilities of better understanding and targeting such inhibitors to have more selective effects on the brain.

These and other features of the present invention will become apparent upon reference to the accompanying figures and upon reading the following detailed description and appended claims.

5. Brief Description of the Drawings

A more particular description of the invention briefly described above will be rendered by reference to the appended figures. These figures only provide information concerning typical embodiments of the invention and are not therefore to be considered limiting of its scope.

Figure 1 shows the structure of mRNAs encoded by the rat *PDE4B* gene. The numbers *1-4* indicate transcripts represented by the following cDNAs: *1*, PDE4B1 (pRPDE89 (SEQ ID NO: 5); GenBank™ AF202732); *2*, PDE4B2 (pRPDE18 (SEQ ID NO: 8); GenBank™ L27058); *3*, PDE4B3 (pRPDE74 (SEQ ID NO: 9); GenBank™ U95748); *4*, PDE4B4 (pRPDE90 (SEQ ID NO: 1) and pRPDE92 (SEQ ID NO: 10); GenBank™ AF202733). The heavy bar indicates sequences homologous to other PDE4 isoforms, with the strongest regions of conservation (the catalytic region and UCR1 and UCR2) indicated by the cross-hatched areas. The thin, branched lines adjacent to the numbers indicate sequence regions unique to each isoform. The thin lines merge where

the sequences of the various isoforms join the shared sequence. Small boxes indicate start codons and the asterisk indicates the common stop codon.

Figure 2 shows an alignment of the amino acid sequences of human PDE4B1 (top, SEQ ID NO: 7) and rat PDE4B1 (bottom, SEQ ID NO: 6). The sequence of human PDE4B1 has been described previously (pTM72 in Bolger, *Mol. Cell Biol.* 13:6558–71 (1993), GenBank™ L20966). The sequence of PDE4B1 was deduced from the pRPDE89 cDNA.

Figure 3 shows an alignment of the amino acid sequences of rat PDE4B1 (SEQ ID NO: 6), PDE4B2 (SEQ ID NO: 8), PDE4B3 (SEQ ID NO: 9), and PDE4B4 (SEQ ID NO: 2). The sequences are derived from the following cDNAs: PDE4B1 (pRPDE89 (SEQ ID NO: 5); GenBank™ AF202732); PDE4B2 (pRPDE18 (SEQ ID NO: 10); GenBank™ L27058); PDE4B3 (pRPDE74 (SEQ ID NO: 11); GenBank™ U95748); PDE4B4 (pRPDE90 and pRPDE92; GenBank™ AF202733).

Figure 4 shows the nucleotide sequence (SEQ ID NO: 1) encoding PDE4B4. The sequences of two plasmids, pRPDE90 and pRPDE92, have been merged. On the merged sequence, pRPDE92 corresponds to nucleotides 1 to 1936, and pRPDE90 corresponds to nucleotides 253 to 2433. This sequence is available as GenBank™ AF202733.

Figure 5 shows the nucleotide sequence of pRPDE89 (SEQ ID NO: 5), which encodes PDE4B1. This sequence is available as GenBank™ AF202732.

6. Detailed Description of the Invention

The present invention provides two novel cAMP-specific phosphodiesterase (PDE4B) isoform cDNAs. These cDNAs encode phosphodiesterases, which function in the regulation of physiological processes by hydrolizing cAMP, an intracellular signaling molecule derived from ATP.

The first cAMP-specific phosphodiesterase isoform cDNA is pRPDE90, a phosphodiesterase isolated from a rat (*Rattus norwegenesis;* Sprague-Dawley strain) cerebral cortex cDNA library cloned into the Eco RI site of Lambda ZAPII, which was obtained from Stratagene. This cDNA encodes a novel PDE4B isoform named PDE4B4 by the inventors in accordance with convention.

PDE4B4 is a novel PDE4B isoform comprising 659 amino acids, 642 of which are shared with the other "long" isoforms of PDE4B: PDE4B1 and PDE4B2. The remaining 17 amino acids are found at the extreme amino-terminal end of the protein.

The second cAMP-specific phosphodiesterase isoform cDNA of the instant invention is pRPDE89, a novel rat cDNA. pRPDE89 encodes a protein comprising 736 amino acids. This protein is identical in length and 96% identical in amino acids to the human PDE4B1 isoform (712 of 736 amino acids are identical). Without being bound to any particular theory, it appears that pRPDE89 encodes the rat counterpart of the human PDE4B1 isoform of PDE4B.

The present invention provides isolated and purified nucleic acid molecules comprising nucleotides that encode the amino acid sequences of SEQ ID NOS: 2, 4, and 6. In certain embodiments, these nucleic acid molecules comprise nucleotides 262 to 2238 of SEQ ID NO: 1, nucleotides 1 to 51 of SEQ ID NO: 3, and nucleotides 325 to 2532 of SEQ ID NO: 5, respectively. The present invention also provides nucleic acid molecules that encode amino acid sequences that are greater than 90%, greater than 85%, greater than 80%, greater than 75%, and greater than 70% identical to SEQ ID NO: 4. The present invention also provides such nucleic acid molecules subcloned into plasmids; such nucleic acid molecules subcloned into prokaryotic or eukaryotic expression vectors; and such nucleic acid molecules stably or transiently incorporated into a prokaryotic or eukaryotic host cell.

The present invention also provides isolated and purified proteins comprising the amino acid sequences of SEQ ID NOS: 2 and 6 and peptides comprising the amino acid sequence of SEQ ID NO: 4. The present invention further provides antibodies that specifically recognize peptides comprising the amino acid sequence of SEQ ID NO: 4. Such antibodies may be polyclonal or monoclonal antibodies that are prepared according to methods that are well-known in the art. *See, e.g.*, Harlow & Lane, *Antibodies: A Laboratory Manual* (1988).

Novel PDE4B isoforms such as those of the instant invention are of importance for several reasons. One reason is that the isoforms of the present invention are expressed in brain—an important potential target of PDE4 inhibitors. Indeed, cDNAs encoding numerous PDE4 isoforms have previously been isolated from brain. *See e.g.*, Bolger et al., *Mol. Cell Biol.* 13:6558–71 (1993), Huston et al., *Biochem J.* 328:549–56 (1997),

McLaughlin et al., *J.Biol.Chem.* 268:6470–76 (1993), Bolger et al., *Gene.* 149:237–44 (1993), Davis et al., *Proc. Natl. Acad. Sci. U.S.A.* 86:3604–08 (1989), Colicelli et al., *Proc. Natl. Acad. Sci. U.S.A.* 86:3599–3603 (1989), and Engels et al., *FEBS Lett.* 358:305–10 (1995). The brain is thus a target for many of the actions of selective PDE4 inhibitors. It is therefore important to determine exactly which PDE4 isoforms are present in the brain.

PDE4 inhibitors have several demonstrated effects in the human brain, several of which are beneficial, and others of which are harmful. Some of the potential beneficial effects of PDE4 inhibitors include a demonstrated anti-depressant action. Fleischhacker et al., *Neuropsychobiology,* 26:59–64 (1992), Eckmann et al., *Current Therapeutic Research,* 43:291–95 (1988). PDE4 inhibitors may also augment memory and other central nervous system functions. However, PDE4 inhibitors can cause nausea and trigger other gastrointestinal side effects. At least a portion of these deleterious side effects are likely mediated by the action of these drugs in the brain.

Discovery of additional isoforms of the PDE4B phosphodiesterases would open greater possibilities for developing inhibitors that could be specifically targeted at one or more isoforms. Such targeting would allow a more viable approach for utilizing the beneficial properties of these inhibitors in clinical treatment, while selectively avoiding negative side effects.

As a result, a search for novel PDE4 isoforms was initiated in rat brain. Two previously unknown PDE4 isoforms were subsequently isolated. While not being bound to any one particular theory, one of these appears to be the rat homolog of the human PDE4B1 isoform, which has been described previously in the art. Bolger et al., *Mol. Cell Biol.* 13:6558–71 (1993). The second novel isoform, called PDE4B4, has a unique 17 amino acid amino-terminal region which is not present in any other PDE4B isoform. It appears likely that PDE4B4 will be similar to other PDE4 isoforms in that it will be highly specific for cAMP and be inhibited by the prototypical PDE4 inhibitor rolipram.

It has previously been shown that the various PDE4 isoforms have different tissue expression patterns. Huston et al., *Biochem J.* 328:549–56 (1997). Indeed, it has even been shown that different isoforms encoded by the same gene may vary substantially in their tissue expression. (Bolger et al., *Mol. Cell Biol.* 13:6558–71 (1993), Bolger et al., *J. Biol. Chem.* 271:1065–71 (1996), and Bolger et al., *Gene.* 149:237–44 (1994). Studies are

in progress to determine the pattern of expression of the four known rat PDE4B isoforms, with special emphasis on their expression in various regions of the brain. Such discoveries and studies create the possibility of exploiting differences in the patterns of tissue expression of the various PDE4 isoforms to "target" the effects of PDE4 inhibitors to specific regions of the brain, thus maximizing their positive effects and minimizing or negating their negative effects.

One current explanation for the divergence of the PDE4B1, PDE4B3 and PDE4B4 mRNAs is alternative mRNA splicing. This has been documented as accounting for the existence of the PDE4A and PDE4D isoforms. Bolger et al., *J.Biol.Chem.* 271:1065–71 (1996), Bolger et al., *Biochem J.* 328:539–48 (1997), and Houslay et al., *Advances in Pharmacology* 44:225–342 (1998). Consistent with this explanation, it has been shown that the point of divergence between PDE4B1, PDE4B3 and PDE4B4 corresponds with the major point of alternative mRNA splicing in the *D. melanogaster dunce* gene transcripts. It also corresponds with the major point of alternative mRNA splicing in alternatively spliced mRNAs from the human *PDE4A* (Bolger et al., *Mol. Cell Biol.* 13:6558–71 (1993)), *PDE4B* (Huston et al., *Biochem J.* 328:549–56 (1997)) and *PDE4D* (Bolger et al., *Biochem J.* 328:539–48 (1997)) genes. It also corresponds to the 5' end of an exon in the human *PDE4A* (Sullivan et al., *Biochem J.* 333:693–703 (1998)) and murine *Pde4a* (Olsen & Bolger, *Mammalian Genome* 11:41-45 (2000)) genes.

In addition, since there is no common 5' region of sequence at the 5' ends of any of these cDNAs, it appears likely that each is generated from a different transcriptional start site. It has been previously demonstrated that several murine *Pde4a* transcripts, including PDE4A5, are generated in this manner (Olsen & Bolger, *Mammalian Genome* 11:41-45 (2000)).

All references, publications, patents, patent applications, and commercial materials cited in this application are hereby incorporated by reference in their entirety.

7. **Examples:**

The following example is given to illustrate an embodiment which has been made within the scope of the present invention. It is to be understood that the following example is neither comprehensive nor exhaustive of the many types of embodiments which can be prepared in accordance with the present invention.

Example 1—Two Novel PDE4B Isoforms

Experimental Techniques:

Materials: A rat (*Rattus norwegenesis*; Sprague-Dawley strain) cerebral cortex cDNA library, cloned into the Eco RI site of Lambda ZAPII, was obtained from Stratagene. All molecular biology, biochemistry and cell culture reagents were from New England Biolabs, Life Technologies or Roche Molecular Systems unless specified otherwise.

Isolation and Analysis of cDNA Clones: Procedures were as described by Sambrook *et al.* (Sambrook et al., *Molecular Cloning: A Laboratory Manual.* (1989)) unless otherwise specified. The cDNA library was screened with a probe corresponding to nucleotides 204 to 1299 of rat PDE4B3 (pRPDE74 (SEQ ID NO: 9) GenBank™ accession number U95748; (Huston et al., *Biochem J.* 328:549–56 (1997)). This region encodes the unique amino-terminal region of PDE4B3 as well as UCR1 and the majority of UCR2 (Fig. 1). Hybridization was performed with a final wash in 0.3 x SSC, 0.3% SDS at 62°C. Sequencing was performed on both strands with an ABI Prism sequencer (Perkin-Elmer) according to the manufacturer's instructions. Alignments were generated with the Gap and Lineup programs of the Wisconsin Package of UNIX sequence software programs (Oxford Molecular Group).

Results:

To obtain cDNAs encoding PDE4B isoforms, a rat cortex cDNA library was screened with a probe corresponding to UCR1 and UCR2 of rat PDE4B3 (Huston et al., *Biochem. J.* 328:549–56 (1997)). This probe was designed to detect all "long" (i.e., UCR1-containing) PDE4B isoforms. cDNAs encoding two different PDE4B isoforms were detected in the screen (see Fig. 1). One cDNA clone, called pRPDE89 (SEQ ID NO: 5), encoded a protein of 736 amino acids (SEQ ID NO: 6). This isoform was identical in length and had greater than 96% amino acid identity (712/736 amino acids identical, Fig. 2) with the human PDE4B1 isoform (SEQ ID NO: 7). Bolger et al., *Mol. Cell Biol.* 13:6558–71 (1993). It was therefore concluded that pRPDE89 encodes the rat PDE4B1 isoform.

Also detected in the screen was a cDNA clone, called pRPDE90 (SEQ ID NO: 1), which encoded the complete open reading frame of a novel PDE4B isoform. This new isoform was called PDE4B4, using the accepted nomenclature. Beavo, *Physiol. Rev.* 75:725–48 (1995). The PDE4B4 protein consists of 659 amino acids (SEQ ID NO: 2), 17

of which are located at the extreme amino-terminal end of the protein and show no detectable homology to any previously cloned PDE4B sequence (SEQ ID NOS: 3, 4). The remaining 642 amino acids are identical to the corresponding regions of the "long" PDE4B isoforms PDE4B1 and PDE4B3 (Fig. 3). The nucleotide sequences of the common regions of PDE4B1, PDE4B3 and PDE4B4 are also identical. The sequence of the novel region of PDE4B4 was confirmed by the sequence of another clone isolated in the screen, called pRPDE92 (SEQ ID NO: 10), which completely overlapped the novel region of pRPDE90 and contained sequence of an additional portion of the 5' untranslated region of the mRNA.

The invention may be embodied in other specific forms without departing from its essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes that come within the meaning and range of equivalency of the claims are to be embraced within their scope.

CLAIMS:

1. An isolated and purified nucleic acid molecule comprising nucleotides encoding the amino acid sequence of SEQ ID NO: 2.
2. The nucleic acid molecule of Claim 1, comprising nucleotides 262 to 2238 of SEQ ID NO: 1.
3. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule is subcloned into a plasmid.
4. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule is subcloned into a prokaryotic or eukaryotic expression vector.
5. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule is stably or transiently incorporated into a prokaryotic or eukaryotic host cell.
6. An isolated and purified protein comprising the amino acid sequence of SEQ ID NO: 2.
7. An isolated and purified nucleic acid molecule comprising nucleotides which code for the amino acid sequence of SEQ ID NO: 4.
8. The nucleic acid molecule of Claim 7, comprising the nucleotide sequence of SEQ ID NO: 3.
9. An isolated and purified nucleic acid molecule comprising a nucleotide sequence that encodes an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 4.
10. An isolated and purified nucleic acid molecule comprising a nucleotide sequence that encodes an amino acid sequence that is at least 75% identical to the amino acid sequence of SEQ ID NO: 4.
11. An isolated and purified peptide comprising the amino acid sequence of SEQ ID NO: 4.
12. An antibody that specifically recognizes the peptide of claim 11.
13. An isolated and purified nucleic acid molecule comprising nucleotides encoding the amino acid sequence of SEQ ID NO: 6.
14. The nucleic acid molecule of Claim 13, comprising nucleotide 325 to 2532 of SEQ ID NO: 5.
15. The nucleic acid molecule of Claim 13, wherein said nucleic acid molecule is subcloned into a plasmid.
16. The nucleic acid molecule of Claim 13, wherein said nucleic acid molecule is

subcloned into a prokaryotic or eukaryotic expression vector.

17. The nucleic acid molecule of Claim 14, wherein said nucleic acid molecule is stably or transiently incorporated into a prokaryotic or eukaryotic host cell.

18. An isolated and purified protein comprising the amino acid sequence of SEQ ID NO: 6.

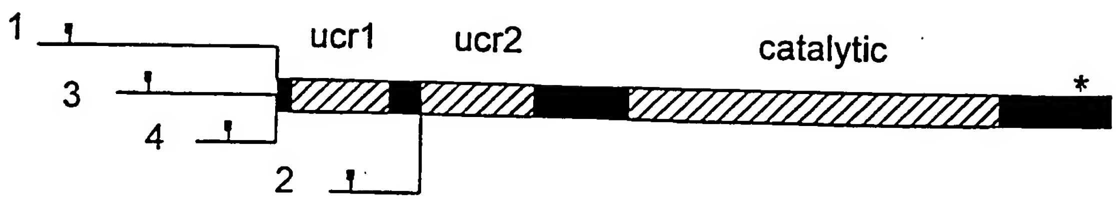
1
3
4
2
ucr1
ucr2
catalytic
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Fig. 2 (two pages in length)

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   1 MKKSRSVMTVMADDNVKDYFECSLSKSYSSSSNTLGIDLWRGRRCCSGNL 50
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   1 MKKSRSVMAVTADDNLKDYFECSLSKSYSSSSYTLGIDLWRGRRCCSGNL 50
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  51 QLPPLSQRQSERARTPEGDGISRPTTLPLTTLPSIAITTVSQECFDVENG 100
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  51 QLPPLSQRQSERARTPEGDGISRPTTLPLTTLPSIAITTVSQECFDVENG 100
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 101 PSPGRSPLDPQASSSAGLVLHATFPGHSQRRESFLYRSDSDYDLSPKAMS 150
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     ||||||||||||||||||||||||||||||||||||||||||||||||||
 551 DRIQVLRNMVHCADLSNPTKSLELYRQWTDRIMEEFFQQGDKERERGMEI 600
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601 SPMCDKHTASVEKSQVGFIDYIVHPLWETWADLVQPDAQDILDTLEDNRN 650
    ||||||||||||||||||||||||||||||||||||||||||||||||||
601 SPMCDKHTASVEKSQVGFIDYIVHPLWETWADLVQPDAQDILDTLEDNRN 650

651 WYQSMIPQSPSPPLDEQNRDCQGLMEKFQFELTLDEEDSEGPEKEGEGHS 700
    ||||||||||||||||..||||||||||||||||:||||||||||||| .
651 WYQSMIPQSPSPPLDERSRDCQGLMEKFQFELTLEEEDSEGPEKEGEGPN 700

701 YFSSTKTLCVIDPENRDSLGETDIDIATEDKSPVDT* 736
    ||||||||||||||||||| |||||||||||| :|||
701 YFSSTKTLCVIDPENRDSLEETDIDIATEDKSLIDT* 736
```

Fig. 3 (two pages in length)

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                1                                                   50
PDE4B3          .......... .....MTAKN SSKELPASES EVCIKTFKEQ MRLELELPKL
PDE4B1          MKKSRSVMAV TADDNLKDYF ECSLSKSYSS SSYTLGIDLW RGRRCCSGNL
PDE4B4          .......... .......... .......... .......... ..........
PDE4B2          .......... .......... .......... .......... ..........

                51                                                 100
PDE4B3          PGNRPTSPKI SPRSSPRNSP CFFRKLLVNK SIRQRRRFTV AHTCFDVENG
PDE4B1          QLPPLSQRQS ERARTPEGDG ISRPTTLPLT TLPSIAITTV SQECFDVENG
PDE4B4          .......... .......... .......MLH VNDLPPPRRH SWICFDVENG
PDE4B2          .......... .......... .......... .......... ..........

                101                                                150
PDE4B3          PSPGRSPLDP QASSSSGLVL HAAFPGHSQR RESFLYRSDS DYDLSPKAMS
PDE4B1          PSPGRSPLDP QASSSSGLVL HAAFPGHSQR RESFLYRSDS DYDLSPKAMS
PDE4B4          PSPGRSPLDP QASSSSGLVL HAAFPGHSQR RESFLYRSDS DYDLSPKAMS
PDE4B2          .......... .......... .......... .......... ..........

                151                                                200
PDE4B3          RNSSLPSEQH GDDLIVTPFA QVLASLRIVR NNFTLLTNLH GAPNKRSPAA
PDE4B1          RNSSLPSEQH GDDLIVTPFA QVLASLRSVR NNFTLLTNLH GAPNKRSPAA
PDE4B4          RNSSLPSEQH GDDLIVTPFA QVLASLRSVR NNFTLLTNLH GAPNKRSPAA
PDE4B2          .......... .......... ..MKEQGGTV SGAGSSRGGG DSAMASLQPL

                201                                                250
PDE4B3          SQAPVTRVSL QEESYQKLAM ETLEELDWCL DQLETIQTYR SVSEMASNKF
PDE4B1          SQAPVTRVSL QEESYQKLAM ETLEELDWCL DQLETIQTYR SVSEMASNKF
PDE4B4          SQAPVTRVSL QEESYQKLAM ETLEELDWCL DQLETIQTYR SVSEMASNKF
PDE4B2          QPNYLSVCLF AEESYQKLAM ETLEELDWCL DQLETIQTYR SVSEMASNKF

                251                                                300
PDE4B3          KRMLNRELTH LSEMSRSGNQ VSEYISNTFL DKQNDVEIPS PTQKDREKKK
PDE4B1          KRMLNRELTH LSEMSRSGNQ VSEYISNTFL DKQNDVEIPS PTQKDREKKK
PDE4B4          KRMLNRELTH LSEMSRSGNQ VSEYISNTFL DKQNDVEIPS PTQKDREKKK
PDE4B2          KRMLNRELTH LSEMSRSGNQ VSEYISNTFL DKQNDVEIPS PTQKDREKKK

                301                                                350
PDE4B3          KQQLMTQISG VKKLMHSSSL NNTSISRFGV NTENEDHLAK ELEDLNKWGL
PDE4B1          KQQLMTQISG VKKLMHSSSL NNTSISRFGV NTENEDHLAK ELEDLNKWGL
PDE4B4          KQQLMTQISG VKKLMHSSSL NNTSISRFGV NTENEDHLAK ELEDLNKWGL
PDE4B2          KQQLMTQISG VKKLMHSSSL NNTSISRFGV NTENEDHLAK ELEDLNKWGL

                351                                                400
PDE4B3          NIFNVAGYSH NRPLTCIMYA IFQERDLLKT FKISSDTFVT YMMTLEDHYH
PDE4B1          NIFNVAGYSH NRPLTCIMYA IFQERDLLKT FKISSDTFVT YMMTLEDHYH
PDE4B4          NIFNVAGYSH NRPLTCIMYA IFQERDLLKT FKISSDTFVT YMMTLEDHYH
PDE4B2          NIFNVAGYSH NRPLTCIMYA IFQERDLLKT FKISSDTFVT YMMTLEDHYH

                401                                                450
PDE4B3          SDVAYHNSLH AADVAQSTHV LLSTPALDAV FTDLEILAAI FAAAIHDVDH
PDE4B1          SDVAYHNSLH AADVAQSTHV LLSTPALDAV FTDLEILAAI FAAAIHDVDH
PDE4B4          SDVAYHNSLH AADVAQSTHV LLSTPALDAV FTDLEILAAI FAAAIHDVDH
PDE4B2          SDVAYHNSLH AADVAQSTHV LLSTPAPDAV FTDLEILAAI FAAAIHDVDH

                451                                                500
PDE4B3          PGVSNQFLIN TNSELALMYN DESVLENHHL AVGFKLLQEE HCDIFQNLTK
PDE4B1          PGVSNQFLIN TNSELALMYN DESVLENHHL AVGFKLLQEE HCDIFQNLTK
PDE4B4          PGVSNQFLIN TNSELALMYN DESVLENHHL AVGFKLLQEE HCDIFQNLTK
PDE4B2          PGVSNQFLIN TNSELALMYN DESVLENHHL AVGFKLLQEE HCDIFQNLTK
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              501                                                      550
PDE4B3        KQRQTLRKMV IDMVLATDMS KHMSLLADLK TMVETKKVTS SGVLLLDNYT
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PDE4B4        KQRQTLRKMV IDMVLATDMS KHMSLLADLK TMVETKKVTS SGVLLLDNYT
PDE4B2        KQRQTLRKMV IDMVLATDMS KHMSLLADLK TMVETKKVTS SGVLLLDNYT

              551                                                      600
PDE4B3        DRIQVLRNMV HCADLSNPTK SLELYRQWTD RIMEEFFQQG DKERERGMEI
PDE4B1        DRIQVLRNMV HCADLSNPTK SLELYRQWTD RIMEEFFQQG DKERERGMEI
PDE4B4        DRIQVLRNMV HCADLSNPTK SLELYRQWTD RIMEEFFQQG DKERERGMEI
PDE4B2        DRIQVLRNMV HCADLSNPTK SLELYRQWTD RIMEEFFQQG DKERERGMEI

              601                                                      650
PDE4B3        SPMCDKHTAS VEKSQVGFID YIVHPLWETW ADLVQPDAQD ILDTLEDNRN
PDE4B1        SPMCDKHTAS VEKSQVGFID YIVHPLWETW ADLVQPDAQD ILDTLEDNRN
PDE4B4        SPMCDKHTAS VEKSQVGFID YIVHPLWETW ADLVQPDAQD ILDTLEDNRN
PDE4B2        SPMCDKHTAS VEKSQVGFID YIVHPLWETW ADLVQPDAQD ILDTLEDNRN

              651                                                      700
PDE4B3        WYQSMIPQSP SPPLDERSRD CQGLMEKFQF ELTLEEEDSE GPEKEGEGPN
PDE4B1        WYQSMIPQSP SPPLDERSRD CQGLMEKFQF ELTLEEEDSE GPEKEGEGPN
PDE4B4        WYQSMIPQSP SPPLDERSRD CQGLMEKFQF ELTLEEEDSE GPEKEGEGPN
PDE4B2        WYQSMIPQSP SPPLDERSRD CQGLMEKFQF ELTLEEEDSE GPEKEGEGPN

              701                                 736
PDE4B3        YFSSTKTLCV IDPENRDSLE ETDIDIATED KSLIDT*
PDE4B1        YFSSTKTLCV IDPENRDSLE ETDIDIATED KSLIDT*
PDE4B4        YFSSTKTLCV IDPENRDSLE ETDIDIATED KSLIDT*
PDE4B2        YFSSTKTLCV IDPENRDSLE ETDIDIATED KSLIDT*
```

Fig. 4

GAATTCGGCACGAGCAATTTCCTCATCTGATTTCTAAAGGAAGCTACTTGCGATGGTCCTCTGCAACCTC
GTGTGTCGATTGCTAAGTCATTGCTACTCGCATTGGAATGATCTCTACCCCGCAATGGAGAGTGGCATGC
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TGCCTCCTCCCAGGCGACACTCGTGGATATGCTTTGATGTGGAAAATGGCCCTTCTCCAGGTCGGAGCCC
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AGAGAGTCTTTTCTCTACAGATCCGACAGCGACTATGACTTGTCACCAAAAGCGATGTCAAGGAACTCCT
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CTTCGTAACCTACATGATGACTTTAGAAGACCATTACCATTCTGATGTGGCGTATCACAACAGCCTGCAC
GCTGCTGACGTGGCCCAGTCAACGCACGTTCTCCTCTCTACGCCAGCACTGGATGCTGTCTTCACAGACC
TGGAAATCCTGGCTGCCATTTTTGCAGCTGCCATCCATGATGTTGATCATCCTGGAGTCTCCAATCAGTT
TCTCATCAATACAAATTCCGAACTTGCTTTGATGTATAATGACGAATCTGTGCTGGAAAACCATCACCTC
GCTGTGGGATTCAAGCTCCTTCAAGAGGAACATTGCGACATCTTTCAGAATCTTACCAAGAAGCAACGCC
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TACATTGTCCATCCATTGTGGGAGACCTGGGCAGACCTGGTTCAGCCTGATGCTCAAGACATTTTGGACA
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GAGCAGGGACTGCCAAGGCCTTATGGAGAAGTTTCAGTTCGAACTGACCCTTGAAGAAGAGGATTCTGAA
GGACCGGAAAAGGAGGGAGAAGGCCCCAACTATTTCAGCAGCACAAAGACACTTTGTGTGATCGATCCAG
AGAACAGGGATTCTCTGGAAGAGACTGACATAGACATTGCCACAGAAGACAAGTCTCTGATCGACACATA
ATCTCCCTCTGTGTGGAGGTGAACATTCTATCCTTGACGAGCATGCCAGCTGAGTGGTAGGGCCCACCTA
CCAGAGCCAAGGCCTGCACAAAACAAAGGCCACCTGGCTTTGCAGTTACTTGAGTTTGGAGCCAGAATGC
AAGGCCGTGAAGCAAATAGCAGTTCCGTGCTGCCTTGCCTTGCCGGCGAGCTT1

Fig. 5

GAATTCGGCACGAGGCGCGGGGGCGGGGGCGGCGTGTAGTGGCAGACGGCCGCAGGGATTATGAATGGGG
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TAATCCTCCAGCCTCGGTGGAGGGAGGCTGCAGCGAGCGCCGGCTGGCAGTAAGGGTTCTTCTGCAAAAG
TCCCCTGCGGTTGCGCGCGTGGAGTGCCGGGGAGCTCGGCCAGGTCTAGTCTGCAGTCAGCAAAGCTGCA
GCAAACAGCAGACATCTCCAGAGGAGCTGTTTGCCACATCTATAATGAAGAAAAGTAGGAGTGTGATGGC
CGTGACTGCAGATGATAATCTTAAGGACTATTTTGAATGTAGCTTGAGTAAATCCTACAGTTCTTCCAGT
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GACGACACTTCCCAGCATTGCTATAACAACTGTAAGCCAGGAGTGCTTTGATGTGGAAAATGGCCCTTCT
CCAGGTCGGAGCCCACTGGACCCTCAAGCCAGCTCTTCTTCAGGACTGGTACTTCATGCCGCCTTCCCTG
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GTCAAGGAACTCCTCACTTCCCAGCGAACAACACGGCGATGACCTGATTGTCACTCCTTTTGCCCAGGTT
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GGTCGCCAGCGGCTAGTCAGGCTCCAGTCACCAGAGTCAGCCTGCAAGAAGAATCATATCAGAAACTAGC
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AGCGAGATGGCTTCAAACAAGTTCAAAAGGATGCTGAACCGGGAGCTGACACACCTCTCAGAGATGAGCA
GATCAGGGAACCAAGTGTCTGAATACATTTCGAACACGTTCTTAGACAAGCAGAACGATGTGGAAATCCC
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AAACTGATGCACAGCTCAAGCCTGAACAACACAAGCATCTCACGCTTTGGAGTCAACACGGAAAATGAGG
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ATGAGCCTCCTGGCTGACCTTAAAACGATGGTAGAAACCAAAAAGGTGACGAGCTCCGGTGTTCTCCTCC
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CAAGTCCTTGGAGTTGTATCGGCAATGGACTGATCGCATCATGGAGGAGTTTTTCCAACAGGGAGACAAA
GAACGGGAGAGGGGAATGGAGATTAGCCCAATGTGTGATAAACACACAGCTTCTGTGGAAAAGTCCCAGG
TTGGTTTCATTGACTACATTGTCCATCCATTGTGGGAGACCTGGGCAGACCTGGTTCAGCCTGATGCTCA
AGACATTTTGGACACACTAGAAGATAACAGGAACTGGTACCAGAGTATGATTCCCCAGAGCCCCTCTCCA
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cgcaatggag agtggcatgc catcagaaag aaaaacgaac ggacaaagag ctcagtagaa     180

actctggcag cgagaacaca gagaaacgca tggagatgag ctaagtcgct gagcggtggg     240

ctgacagtgt accggttcag g atg ttg cac gtg aac gac ttg cct cct ccc       291
                        Met Leu His Val Asn Asp Leu Pro Pro Pro
                        1               5                   10

agg cga cac tcg tgg ata tgc ttt gat gtg gaa aat ggc cct tct cca       339
Arg Arg His Ser Trp Ile Cys Phe Asp Val Glu Asn Gly Pro Ser Pro
                15                  20                  25

ggt cgg agc cca ctg gac cct caa gcc agc tct tct tca gga ctg gta       387
Gly Arg Ser Pro Leu Asp Pro Gln Ala Ser Ser Ser Ser Gly Leu Val
            30                  35                  40

ctt cat gcc gcc ttc cct ggg cac agc caa cgc aga gag tct ttt ctc       435
Leu His Ala Ala Phe Pro Gly His Ser Gln Arg Arg Glu Ser Phe Leu
        45                  50                  55

tac aga tcc gac agc gac tat gac ttg tca cca aaa gcg atg tca agg       483
Tyr Arg Ser Asp Ser Asp Tyr Asp Leu Ser Pro Lys Ala Met Ser Arg
    60                  65                  70

aac tcc tca ctt ccc agc gaa caa cac ggc gat gac ctg att gtc act       531
Asn Ser Ser Leu Pro Ser Glu Gln His Gly Asp Asp Leu Ile Val Thr
75                  80                  85                  90

cct ttt gcc cag gtt ctt gcc agc ttg cga agc gta aga aac aat ttc       579
Pro Phe Ala Gln Val Leu Ala Ser Leu Arg Ser Val Arg Asn Asn Phe
                95                  100                 105
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acc ctg ctg aca aac ctt cac gga gca ccg aac aag agg tcg cca gcg      627
Thr Leu Leu Thr Asn Leu His Gly Ala Pro Asn Lys Arg Ser Pro Ala
            110                 115                 120

gct agt cag gct cca gtc acc aga gtc agc ctg caa gaa gaa tca tat      675
Ala Ser Gln Ala Pro Val Thr Arg Val Ser Leu Gln Glu Glu Ser Tyr
        125                 130                 135

cag aaa cta gca atg gag acg ctg gag gaa cta gac tgg tgc cta gac      723
Gln Lys Leu Ala Met Glu Thr Leu Glu Glu Leu Asp Trp Cys Leu Asp
    140                 145                 150

cag cta gag acc atc cag acc tac cgc tct gtc agc gag atg gct tca      771
Gln Leu Glu Thr Ile Gln Thr Tyr Arg Ser Val Ser Glu Met Ala Ser
155                 160                 165                 170

aac aag ttc aaa agg atg ctg aac cgg gag ctg aca cac ctc tca gag      819
Asn Lys Phe Lys Arg Met Leu Asn Arg Glu Leu Thr His Leu Ser Glu
                175                 180                 185

atg agc aga tca ggg aac caa gtg tct gaa tac att tcg aac acg ttc      867
Met Ser Arg Ser Gly Asn Gln Val Ser Glu Tyr Ile Ser Asn Thr Phe
            190                 195                 200

tta gac aag cag aac gat gtg gaa atc cca tct ccc acc cag aag gac      915
Leu Asp Lys Gln Asn Asp Val Glu Ile Pro Ser Pro Thr Gln Lys Asp
        205                 210                 215

agg gag aag aag aag aag cag cag ctc atg acc cag ata agt gga gtg      963
Arg Glu Lys Lys Lys Lys Gln Gln Leu Met Thr Gln Ile Ser Gly Val
    220                 225                 230

aag aaa ctg atg cac agc tca agc ctg aac aac aca agc atc tca cgc      1011
Lys Lys Leu Met His Ser Ser Ser Leu Asn Asn Thr Ser Ile Ser Arg
235                 240                 245                 250

ttt gga gtc aac acg gaa aat gag gat cat cta gcc aag gag ctg gaa      1059
Phe Gly Val Asn Thr Glu Asn Glu Asp His Leu Ala Lys Glu Leu Glu
                255                 260                 265

gac ctg aac aaa tgg ggc ctt aac atc ttc aac gtg gct ggg tac tcc      1107
Asp Leu Asn Lys Trp Gly Leu Asn Ile Phe Asn Val Ala Gly Tyr Ser
            270                 275                 280

cat aat cgg ccc ctc aca tgc atc atg tac gcc att ttc cag gaa aga      1155
His Asn Arg Pro Leu Thr Cys Ile Met Tyr Ala Ile Phe Gln Glu Arg
        285                 290                 295

gac ctt cta aag acg ttt aaa atc tcc tcc gac acc ttc gta acc tac      1203
Asp Leu Leu Lys Thr Phe Lys Ile Ser Ser Asp Thr Phe Val Thr Tyr
    300                 305                 310

atg atg act tta gaa gac cat tac cat tct gat gtg gcg tat cac aac      1251
Met Met Thr Leu Glu Asp His Tyr His Ser Asp Val Ala Tyr His Asn
315                 320                 325                 330

agc ctg cac gct gct gac gtg gcc cag tca acg cac gtt ctc ctc tct      1299
Ser Leu His Ala Ala Asp Val Ala Gln Ser Thr His Val Leu Leu Ser
                335                 340                 345
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acg cca gca ctg gat gct gtc ttc aca gac ctg gaa atc ctg gct gcc     1347
Thr Pro Ala Leu Asp Ala Val Phe Thr Asp Leu Glu Ile Leu Ala Ala
            350                 355                 360

att ttt gca gct gcc atc cat gat gtt gat cat cct gga gtc tcc aat     1395
Ile Phe Ala Ala Ala Ile His Asp Val Asp His Pro Gly Val Ser Asn
        365                 370                 375

cag ttt ctc atc aat aca aat tcc gaa ctt gct ttg atg tat aat gac     1443
Gln Phe Leu Ile Asn Thr Asn Ser Glu Leu Ala Leu Met Tyr Asn Asp
    380                 385                 390

gaa tct gtg ctg gaa aac cat cac ctc gct gtg gga ttc aag ctc ctt     1491
Glu Ser Val Leu Glu Asn His His Leu Ala Val Gly Phe Lys Leu Leu
395                 400                 405                 410

caa gag gaa cat tgc gac atc ttt cag aat ctt acc aag aag caa cgc     1539
Gln Glu Glu His Cys Asp Ile Phe Gln Asn Leu Thr Lys Lys Gln Arg
                415                 420                 425

cag aca ctc agg aaa atg gtg att gac atg gtg tta gca act gat atg     1587
Gln Thr Leu Arg Lys Met Val Ile Asp Met Val Leu Ala Thr Asp Met
            430                 435                 440

tcc aag cac atg agc ctc ctg gct gac ctt aaa acg atg gta gaa acc     1635
Ser Lys His Met Ser Leu Leu Ala Asp Leu Lys Thr Met Val Glu Thr
        445                 450                 455

aaa aag gtg acg agc tcc ggt gtt ctc ctc ctg gac aac tat act gac     1683
Lys Lys Val Thr Ser Ser Gly Val Leu Leu Leu Asp Asn Tyr Thr Asp
    460                 465                 470

cgg ata cag gtt ctt cgc aac atg gta cat tgt gca gac ctg agc aac     1731
Arg Ile Gln Val Leu Arg Asn Met Val His Cys Ala Asp Leu Ser Asn
475                 480                 485                 490

cct acc aag tcc ttg gag ttg tat cgg caa tgg act gat cgc atc atg     1779
Pro Thr Lys Ser Leu Glu Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met
                495                 500                 505

gag gag ttt ttc caa cag gga gac aaa gaa cgg gag agg gga atg gag     1827
Glu Glu Phe Phe Gln Gln Gly Asp Lys Glu Arg Glu Arg Gly Met Glu
            510                 515                 520

att agc cca atg tgt gat aaa cac aca gct tct gtg gaa aag tcc cag     1875
Ile Ser Pro Met Cys Asp Lys His Thr Ala Ser Val Glu Lys Ser Gln
        525                 530                 535

gtt ggt ttc att gac tac att gtc cat cca ttg tgg gag acc tgg gca     1923
Val Gly Phe Ile Asp Tyr Ile Val His Pro Leu Trp Glu Thr Trp Ala
    540                 545                 550

gac ctg gtt cag cct gat gct caa gac att ttg gac aca cta gaa gat     1971
Asp Leu Val Gln Pro Asp Ala Gln Asp Ile Leu Asp Thr Leu Glu Asp
555                 560                 565                 570

aac agg aac tgg tac cag agt atg att ccc cag agc ccc tct cca cca     2019
Asn Arg Asn Trp Tyr Gln Ser Met Ile Pro Gln Ser Pro Ser Pro Pro
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ctg gac gag agg agc agg gac tgc caa ggc ctt atg gag aag ttt cag     2067
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Leu Asp Glu Arg Ser Arg Asp Cys Gln Gly Leu Met Glu Lys Phe Gln
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Phe Glu Leu Thr Leu Glu Glu Glu Asp Ser Glu Gly Pro Glu Lys Glu
        605                 610                 615

gga gaa ggc ccc aac tat ttc agc agc aca aag aca ctt tgt gtg atc      2163
Gly Glu Gly Pro Asn Tyr Phe Ser Ser Thr Lys Thr Leu Cys Val Ile
    620                 625                 630

gat cca gag aac agg gat tct ctg gaa gag act gac ata gac att gcc      2211
Asp Pro Glu Asn Arg Asp Ser Leu Glu Glu Thr Asp Ile Asp Ile Ala
635                 640                 645                 650

aca gaa gac aag tct ctg atc gac aca taatctccct ctgtgtggag            2258
Thr Glu Asp Lys Ser Leu Ile Asp Thr
                655

gtgaacattc tatccttgac gagcatgcca gctgagtggt agggcccacc taccagagcc    2318

aaggcctgca caaaacaaag gccacctggc tttgcagtta cttgagtttg gagccagaat    2378

gcaaggccgt gaagcaaata gcagttccgt gctgccttgc cttgccggcg agctt         2433


<210>  2
<211>  659
<212>  PRT
<213>  Rattus norvegicus

<400>  2

Met Leu His Val Asn Asp Leu Pro Pro Pro Arg Arg His Ser Trp Ile
1               5                   10                  15

Cys Phe Asp Val Glu Asn Gly Pro Ser Pro Gly Arg Ser Pro Leu Asp
            20                  25                  30

Pro Gln Ala Ser Ser Ser Ser Gly Leu Val Leu His Ala Ala Phe Pro
        35                  40                  45

Gly His Ser Gln Arg Arg Glu Ser Phe Leu Tyr Arg Ser Asp Ser Asp
    50                  55                  60

Tyr Asp Leu Ser Pro Lys Ala Met Ser Arg Asn Ser Ser Leu Pro Ser
65                  70                  75                  80

Glu Gln His Gly Asp Asp Leu Ile Val Thr Pro Phe Ala Gln Val Leu
                85                  90                  95

Ala Ser Leu Arg Ser Val Arg Asn Asn Phe Thr Leu Leu Thr Asn Leu
            100                 105                 110
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His Gly Ala Pro Asn Lys Arg Ser Pro Ala Ala Ser Gln Ala Pro Val
        115                 120                 125

Thr Arg Val Ser Leu Gln Glu Glu Ser Tyr Gln Lys Leu Ala Met Glu
    130                 135                 140

Thr Leu Glu Glu Leu Asp Trp Cys Leu Asp Gln Leu Glu Thr Ile Gln
145                 150                 155                 160

Thr Tyr Arg Ser Val Ser Glu Met Ala Ser Asn Lys Phe Lys Arg Met
                165                 170                 175

Leu Asn Arg Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser Gly Asn
            180                 185                 190

Gln Val Ser Glu Tyr Ile Ser Asn Thr Phe Leu Asp Lys Gln Asn Asp
        195                 200                 205

Val Glu Ile Pro Ser Pro Thr Gln Lys Asp Arg Glu Lys Lys Lys Lys
    210                 215                 220

Gln Gln Leu Met Thr Gln Ile Ser Gly Val Lys Lys Leu Met His Ser
225                 230                 235                 240

Ser Ser Leu Asn Asn Thr Ser Ile Ser Arg Phe Gly Val Asn Thr Glu
                245                 250                 255

Asn Glu Asp His Leu Ala Lys Glu Leu Glu Asp Leu Asn Lys Trp Gly
            260                 265                 270

Leu Asn Ile Phe Asn Val Ala Gly Tyr Ser His Asn Arg Pro Leu Thr
        275                 280                 285

Cys Ile Met Tyr Ala Ile Phe Gln Glu Arg Asp Leu Leu Lys Thr Phe
    290                 295                 300

Lys Ile Ser Ser Asp Thr Phe Val Thr Tyr Met Met Thr Leu Glu Asp
305                 310                 315                 320

His Tyr His Ser Asp Val Ala Tyr His Asn Ser Leu His Ala Ala Asp
                325                 330                 335

Val Ala Gln Ser Thr His Val Leu Leu Ser Thr Pro Ala Leu Asp Ala
            340                 345                 350

Val Phe Thr Asp Leu Glu Ile Leu Ala Ala Ile Phe Ala Ala Ala Ile
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355 360 365

His Asp Val Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr
370 375 380

Asn Ser Glu Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu Asn
385 390 395 400

His His Leu Ala Val Gly Phe Lys Leu Leu Gln Glu Glu His Cys Asp
405 410 415

Ile Phe Gln Asn Leu Thr Lys Lys Gln Arg Gln Thr Leu Arg Lys Met
420 425 430

Val Ile Asp Met Val Leu Ala Thr Asp Met Ser Lys His Met Ser Leu
435 440 445

Leu Ala Asp Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser Ser
450 455 460

Gly Val Leu Leu Leu Asp Asn Tyr Thr Asp Arg Ile Gln Val Leu Arg
465 470 475 480

Asn Met Val His Cys Ala Asp Leu Ser Asn Pro Thr Lys Ser Leu Glu
485 490 495

Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe Gln Gln
500 505 510

Gly Asp Lys Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys Asp
515 520 525

Lys His Thr Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr
530 535 540

Ile Val His Pro Leu Trp Glu Thr Trp Ala Asp Leu Val Gln Pro Asp
545 550 555 560

Ala Gln Asp Ile Leu Asp Thr Leu Glu Asp Asn Arg Asn Trp Tyr Gln
565 570 575

Ser Met Ile Pro Gln Ser Pro Ser Pro Pro Leu Asp Glu Arg Ser Arg
580 585 590

Asp Cys Gln Gly Leu Met Glu Lys Phe Gln Phe Glu Leu Thr Leu Glu
595 600 605

Glu Glu Asp Ser Glu Gly Pro Glu Lys Glu Gly Glu Gly Pro Asn Tyr
    610   615   620

Phe Ser Ser Thr Lys Thr Leu Cys Val Ile Asp Pro Glu Asn Arg Asp
625   630   635   640

Ser Leu Glu Glu Thr Asp Ile Asp Ile Ala Thr Glu Asp Lys Ser Leu
                645   650   655

Ile Asp Thr

<210> 3
<211> 51
<212> DNA
<213> Rattus norvegicus

<220>
<221> CDS
<222> (1)..(51)

<400> 3
atg ttg cac gtg aac gac ttg cct cct ccc agg cga cac tcg tgg ata 48
Met Leu His Val Asn Asp Leu Pro Pro Pro Arg Arg His Ser Trp Ile
1   5   10   15

tgc 51
Cys

<210> 4
<211> 17
<212> PRT
<213> Rattus norvegicus

<400> 4

Met Leu His Val Asn Asp Leu Pro Pro Pro Arg Arg His Ser Trp Ile
1   5   10   15

Cys

<210> 5
<211> 3022
<212> DNA
<213> Rattus norvegicus

<220>
<221> CDS
<222> (325)..(2532)

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<400>  5
gaattcggca cgaggcgcgg gggcgggggc ggcgtgtagt ggcagacggc cgcagggatt      60

atgaatgggg gtgggggccg gcgagttgag gttccacccg ggatcgtccg caccggctga     120

tgggcacgca gggctgcgtg taatcctcca gcctcggtgg agggaggctg cagcgagcgc     180

cggctggcag taagggttct tctgcaaaag tcccctgcgg ttgcgcgcgt ggagtgccgg     240

ggagctcggc caggtctagt ctgcagtcag caaagctgca gcaaacagca gacatctcca     300

gaggagctgt ttgccacatc tata atg aag aaa agt agg agt gtg atg gcc        351
                           Met Lys Lys Ser Arg Ser Val Met Ala
                           1               5

gtg act gca gat gat aat ctt aag gac tat ttt gaa tgt agc ttg agt       399
Val Thr Ala Asp Asp Asn Leu Lys Asp Tyr Phe Glu Cys Ser Leu Ser
10                  15                  20                  25

aaa tcc tac agt tct tcc agt tat acc ctt ggg att gac ctc tgg aga       447
Lys Ser Tyr Ser Ser Ser Ser Tyr Thr Leu Gly Ile Asp Leu Trp Arg
                30                  35                  40

ggc aga agg tgc tgt tca gga aac tta cag ttg cca cca ttg tcc cag       495
Gly Arg Arg Cys Cys Ser Gly Asn Leu Gln Leu Pro Pro Leu Ser Gln
            45                  50                  55

aga caa agt gaa agg gca agg aca cct gag gga gat ggc att tcc agg       543
Arg Gln Ser Glu Arg Ala Arg Thr Pro Glu Gly Asp Gly Ile Ser Arg
        60                  65                  70

cca acc acg cta cct ttg acg aca ctt ccc agc att gct ata aca act       591
Pro Thr Thr Leu Pro Leu Thr Thr Leu Pro Ser Ile Ala Ile Thr Thr
    75                  80                  85

gta agc cag gag tgc ttt gat gtg gaa aat ggc cct tct cca ggt cgg       639
Val Ser Gln Glu Cys Phe Asp Val Glu Asn Gly Pro Ser Pro Gly Arg
90                  95                  100                 105

agc cca ctg gac cct caa gcc agc tct tct tca gga ctg gta ctt cat       687
Ser Pro Leu Asp Pro Gln Ala Ser Ser Ser Ser Gly Leu Val Leu His
                110                 115                 120

gcc gcc ttc cct ggg cac agc caa cgc aga gag tct ttt ctc tac aga       735
Ala Ala Phe Pro Gly His Ser Gln Arg Arg Glu Ser Phe Leu Tyr Arg
            125                 130                 135

tcc gac agc gac tat gac ttg tca cca aaa gcg atg tca agg aac tcc       783
Ser Asp Ser Asp Tyr Asp Leu Ser Pro Lys Ala Met Ser Arg Asn Ser
        140                 145                 150

tca ctt ccc agc gaa caa cac ggc gat gac ctg att gtc act cct ttt       831
Ser Leu Pro Ser Glu Gln His Gly Asp Asp Leu Ile Val Thr Pro Phe
    155                 160                 165

gcc cag gtt ctt gcc agc ttg cga agc gta aga aac aat ttc acc ctg       879
Ala Gln Val Leu Ala Ser Leu Arg Ser Val Arg Asn Asn Phe Thr Leu
170                 175                 180                 185

ctg aca aac ctt cac gga gca ccg aac aag agg tcg cca gcg gct agt       927
Leu Thr Asn Leu His Gly Ala Pro Asn Lys Arg Ser Pro Ala Ala Ser
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190 195 200

cag gct cca gtc acc aga gtc agc ctg caa gaa gaa tca tat cag aaa 975
Gln Ala Pro Val Thr Arg Val Ser Leu Gln Glu Glu Ser Tyr Gln Lys
205 210 215

cta gca atg gag acg ctg gag gaa cta gac tgg tgc cta gac cag cta 1023
Leu Ala Met Glu Thr Leu Glu Glu Leu Asp Trp Cys Leu Asp Gln Leu
220 225 230

gag acc atc cag acc tac cgc tct gtc agc gag atg gct tca aac aag 1071
Glu Thr Ile Gln Thr Tyr Arg Ser Val Ser Glu Met Ala Ser Asn Lys
235 240 245

ttc aaa agg atg ctg aac cgg gag ctg aca cac ctc tca gag atg agc 1119
Phe Lys Arg Met Leu Asn Arg Glu Leu Thr His Leu Ser Glu Met Ser
250 255 260 265

aga tca ggg aac caa gtg tct gaa tac att tcg aac acg ttc tta gac 1167
Arg Ser Gly Asn Gln Val Ser Glu Tyr Ile Ser Asn Thr Phe Leu Asp
270 275 280

aag cag aac gat gtg gaa atc cca tct ccc acc cag aag gac agg gag 1215
Lys Gln Asn Asp Val Glu Ile Pro Ser Pro Thr Gln Lys Asp Arg Glu
285 290 295

aag aag aag aag cag cag ctc atg acc cag ata agt gga gtg aag aaa 1263
Lys Lys Lys Lys Gln Gln Leu Met Thr Gln Ile Ser Gly Val Lys Lys
300 305 310

ctg atg cac agc tca agc ctg aac aac aca agc atc tca cgc ttt gga 1311
Leu Met His Ser Ser Ser Leu Asn Asn Thr Ser Ile Ser Arg Phe Gly
315 320 325

gtc aac acg gaa aat gag gat cat cta gcc aag gag ctg gaa gac ctg 1359
Val Asn Thr Glu Asn Glu Asp His Leu Ala Lys Glu Leu Glu Asp Leu
330 335 340 345

aac aaa tgg ggc ctt aac atc ttc aac gtg gct ggg tac tcc cat aat 1407
Asn Lys Trp Gly Leu Asn Ile Phe Asn Val Ala Gly Tyr Ser His Asn
350 355 360

cgg ccc ctc aca tgc atc atg tac gcc att ttc cag gaa aga gac ctt 1455
Arg Pro Leu Thr Cys Ile Met Tyr Ala Ile Phe Gln Glu Arg Asp Leu
365 370 375

cta aag acg ttt aaa atc tcc tcc gac acc ttc gta acc tac atg atg 1503
Leu Lys Thr Phe Lys Ile Ser Ser Asp Thr Phe Val Thr Tyr Met Met
380 385 390

act tta gaa gac cat tac cat tct gat gtg gcg tat cac aac agc ctg 1551
Thr Leu Glu Asp His Tyr His Ser Asp Val Ala Tyr His Asn Ser Leu
395 400 405

cac gct gct gac gtg gcc cag tca acg cac gtt ctc ctc tct acg cca 1599
His Ala Ala Asp Val Ala Gln Ser Thr His Val Leu Leu Ser Thr Pro
410 415 420 425

gca ctg gat gct gtc ttc aca gac ctg gaa atc ctg gct gcc att ttt 1647
Ala Leu Asp Ala Val Phe Thr Asp Leu Glu Ile Leu Ala Ala Ile Phe
430 435 440

gca gct gcc atc cat gat gtt gat cat cct gga gtc tcc aat cag ttt 1695
Ala Ala Ala Ile His Asp Val Asp His Pro Gly Val Ser Asn Gln Phe
445 450 455

ctc atc aat aca aat tcc gaa ctt gct ttg atg tat aat gac gaa tct 1743
Leu Ile Asn Thr Asn Ser Glu Leu Ala Leu Met Tyr Asn Asp Glu Ser
460 465 470

gtg ctg gaa aac cat cac ctc gct gtg gga ttc aag ctc ctt caa gag 1791
Val Leu Glu Asn His His Leu Ala Val Gly Phe Lys Leu Leu Gln Glu
475 480 485

gaa cat tgc gac atc ttt cag aat ctt acc aag aag caa cgc cag aca 1839
Glu His Cys Asp Ile Phe Gln Asn Leu Thr Lys Lys Gln Arg Gln Thr
490 495 500 505

ctc agg aaa atg gtg att gac atg gtg tta gca act gat atg tcc aag 1887
Leu Arg Lys Met Val Ile Asp Met Val Leu Ala Thr Asp Met Ser Lys
510 515 520

cac atg agc ctc ctg gct gac ctt aaa acg atg gta gaa acc aaa aag 1935
His Met Ser Leu Leu Ala Asp Leu Lys Thr Met Val Glu Thr Lys Lys
525 530 535

gtg acg agc tcc ggt gtt ctc ctc ctg gac aac tat act gac cgg ata 1983
Val Thr Ser Ser Gly Val Leu Leu Leu Asp Asn Tyr Thr Asp Arg Ile
540 545 550

cag gtt ctt cgc aac atg gta cat tgt gca gac ctg agc aac cct acc 2031
Gln Val Leu Arg Asn Met Val His Cys Ala Asp Leu Ser Asn Pro Thr
555 560 565

aag tcc ttg gag ttg tat cgg caa tgg act gat cgc atc atg gag gag 2079
Lys Ser Leu Glu Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met Glu Glu
570 575 580 585

ttt ttc caa cag gga gac aaa gaa cgg gag agg gga atg gag att agc 2127
Phe Phe Gln Gln Gly Asp Lys Glu Arg Glu Arg Gly Met Glu Ile Ser
590 595 600

cca atg tgt gat aaa cac aca gct tct gtg gaa aag tcc cag gtt ggt 2175
Pro Met Cys Asp Lys His Thr Ala Ser Val Glu Lys Ser Gln Val Gly
605 610 615

ttc att gac tac att gtc cat cca ttg tgg gag acc tgg gca gac ctg 2223
Phe Ile Asp Tyr Ile Val His Pro Leu Trp Glu Thr Trp Ala Asp Leu
620 625 630

gtt cag cct gat gct caa gac att ttg gac aca cta gaa gat aac agg 2271
Val Gln Pro Asp Ala Gln Asp Ile Leu Asp Thr Leu Glu Asp Asn Arg
635 640 645

aac tgg tac cag agt atg att ccc cag agc ccc tct cca cca ctg gac 2319
Asn Trp Tyr Gln Ser Met Ile Pro Gln Ser Pro Ser Pro Pro Leu Asp
650 655 660 665

gag agg agc agg gac tgc caa ggc ctt atg gag aag ttt cag ttc gaa 2367
Glu Arg Ser Arg Asp Cys Gln Gly Leu Met Glu Lys Phe Gln Phe Glu
670 675 680

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ctg acc ctt gaa gaa gag gat tct gaa gga ccg gaa aag gag gga gaa      2415
Leu Thr Leu Glu Glu Glu Asp Ser Glu Gly Pro Glu Lys Glu Gly Glu
            685                 690                 695

ggc ccc aac tat ttc agc agc aca aag aca ctt tgt gtg atc gat cca      2463
Gly Pro Asn Tyr Phe Ser Ser Thr Lys Thr Leu Cys Val Ile Asp Pro
        700                 705                 710

gag aac agg gat tct ctg gaa gag act gac ata gac att gcc aca gaa      2511
Glu Asn Arg Asp Ser Leu Glu Glu Thr Asp Ile Asp Ile Ala Thr Glu
    715                 720                 725

gac aag tct ctg atc gac aca taatctccct ctgtgtggag gtgaacattc         2562
Asp Lys Ser Leu Ile Asp Thr
730                 735

tatccttgac gagcatgcca gctgagtggt agggcccacc taccagagcc aaggcctgca    2622

caaaacaaag gccacctggc ctttgcagtt acttgagttt ggagccagaa tgcaaggccg    2682

tgaagcaaat agcagttccg tgctgccttg ccttgccggc gagcttggcg gagacccgca    2742

gctgtagtag aagccagttc ccagcacagc taaatggctt gaaaacagag gacagaaagc    2802

tgagagattg ctctgcaata ggtgttgagg ggctgtcccg acaggtgact gaactcacta    2862

acaacttcat ctataaatct cacccatcct gttgtctgcc aacctgtgtg cctttttttgt   2922

aaaatgtttt cgtgtctttg aaatgcctgt tgaatatcta gagtttagta cctccttcta    2982

caaacttttt tgagtctttc tgggaaaaaa aaacctgcag                          3022

&lt;210&gt;  6
&lt;211&gt;  736
&lt;212&gt;  PRT
&lt;213&gt;  Rattus norvegicus

&lt;400&gt;  6

Met Lys Lys Ser Arg Ser Val Met Ala Val Thr Ala Asp Asp Asn Leu
1               5                   10                  15

Lys Asp Tyr Phe Glu Cys Ser Leu Ser Lys Ser Tyr Ser Ser Ser Ser
            20                  25                  30

Tyr Thr Leu Gly Ile Asp Leu Trp Arg Gly Arg Arg Cys Cys Ser Gly
        35                  40                  45

Asn Leu Gln Leu Pro Pro Leu Ser Gln Arg Gln Ser Glu Arg Ala Arg
    50                  55                  60

Thr Pro Glu Gly Asp Gly Ile Ser Arg Pro Thr Thr Leu Pro Leu Thr
65                  70                  75                  80

Thr Leu Pro Ser Ile Ala Ile Thr Thr Val Ser Gln Glu Cys Phe Asp
```

85 90 95

Val Glu Asn Gly Pro Ser Pro Gly Arg Ser Pro Leu Asp Pro Gln Ala
100 105 110

Ser Ser Ser Ser Gly Leu Val Leu His Ala Ala Phe Pro Gly His Ser
115 120 125

Gln Arg Arg Glu Ser Phe Leu Tyr Arg Ser Asp Ser Asp Tyr Asp Leu
130 135 140

Ser Pro Lys Ala Met Ser Arg Asn Ser Ser Leu Pro Ser Glu Gln His
145 150 155 160

Gly Asp Asp Leu Ile Val Thr Pro Phe Ala Gln Val Leu Ala Ser Leu
165 170 175

Arg Ser Val Arg Asn Asn Phe Thr Leu Leu Thr Asn Leu His Gly Ala
180 185 190

Pro Asn Lys Arg Ser Pro Ala Ala Ser Gln Ala Pro Val Thr Arg Val
195 200 205

Ser Leu Gln Glu Glu Ser Tyr Gln Lys Leu Ala Met Glu Thr Leu Glu
210 215 220

Glu Leu Asp Trp Cys Leu Asp Gln Leu Glu Thr Ile Gln Thr Tyr Arg
225 230 235 240

Ser Val Ser Glu Met Ala Ser Asn Lys Phe Lys Arg Met Leu Asn Arg
245 250 255

Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser Gly Asn Gln Val Ser
260 265 270

Glu Tyr Ile Ser Asn Thr Phe Leu Asp Lys Gln Asn Asp Val Glu Ile
275 280 285

Pro Ser Pro Thr Gln Lys Asp Arg Glu Lys Lys Lys Lys Gln Gln Leu
290 295 300

Met Thr Gln Ile Ser Gly Val Lys Lys Leu Met His Ser Ser Ser Leu
305 310 315 320

Asn Asn Thr Ser Ile Ser Arg Phe Gly Val Asn Thr Glu Asn Glu Asp
325 330 335

His Leu Ala Lys Glu Leu Glu Asp Leu Asn Lys Trp Gly Leu Asn Ile
340 345 350

Phe Asn Val Ala Gly Tyr Ser His Asn Arg Pro Leu Thr Cys Ile Met
355 360 365

Tyr Ala Ile Phe Gln Glu Arg Asp Leu Leu Lys Thr Phe Lys Ile Ser
370 375 380

Ser Asp Thr Phe Val Thr Tyr Met Met Thr Leu Glu Asp His Tyr His
385 390 395 400

Ser Asp Val Ala Tyr His Asn Ser Leu His Ala Ala Asp Val Ala Gln
405 410 415

Ser Thr His Val Leu Leu Ser Thr Pro Ala Leu Asp Ala Val Phe Thr
420 425 430

Asp Leu Glu Ile Leu Ala Ala Ile Phe Ala Ala Ala Ile His Asp Val
435 440 445

Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr Asn Ser Glu
450 455 460

Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu Asn His His Leu
465 470 475 480

Ala Val Gly Phe Lys Leu Leu Gln Glu Glu His Cys Asp Ile Phe Gln
485 490 495

Asn Leu Thr Lys Lys Gln Arg Gln Thr Leu Arg Lys Met Val Ile Asp
500 505 510

Met Val Leu Ala Thr Asp Met Ser Lys His Met Ser Leu Leu Ala Asp
515 520 525

Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser Ser Gly Val Leu
530 535 540

Leu Leu Asp Asn Tyr Thr Asp Arg Ile Gln Val Leu Arg Asn Met Val
545 550 555 560

His Cys Ala Asp Leu Ser Asn Pro Thr Lys Ser Leu Glu Leu Tyr Arg
565 570 575

Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe Gln Gln Gly Asp Lys
580 585 590

Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys Asp Lys His Thr
595 600 605

Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr Ile Val His
610 615 620

Pro Leu Trp Glu Thr Trp Ala Asp Leu Val Gln Pro Asp Ala Gln Asp
625 630 635 640

Ile Leu Asp Thr Leu Glu Asp Asn Arg Asn Trp Tyr Gln Ser Met Ile
645 650 655

Pro Gln Ser Pro Ser Pro Pro Leu Asp Glu Arg Ser Arg Asp Cys Gln
660 665 670

Gly Leu Met Glu Lys Phe Gln Phe Glu Leu Thr Leu Glu Glu Glu Asp
675 680 685

Ser Glu Gly Pro Glu Lys Glu Gly Glu Gly Pro Asn Tyr Phe Ser Ser
690 695 700

Thr Lys Thr Leu Cys Val Ile Asp Pro Glu Asn Arg Asp Ser Leu Glu
705 710 715 720

Glu Thr Asp Ile Asp Ile Ala Thr Glu Asp Lys Ser Leu Ile Asp Thr
725 730 735

<210> 7
<211> 736
<212> PRT
<213> Homo sapiens

<400> 7

Met Lys Lys Ser Arg Ser Val Met Thr Val Met Ala Asp Asp Asn Val
1 5 10 15

Lys Asp Tyr Phe Glu Cys Ser Leu Ser Lys Ser Tyr Ser Ser Ser Ser
20 25 30

Asn Thr Leu Gly Ile Asp Leu Trp Arg Gly Arg Arg Cys Cys Ser Gly
35 40 45

Asn Leu Gln Leu Pro Pro Leu Ser Gln Arg Gln Ser Glu Arg Ala Arg
50 55 60

Thr Pro Glu Gly Asp Gly Ile Ser Arg Pro Thr Thr Leu Pro Leu Thr

65 70 75 80

Thr Leu Pro Ser Ile Ala Ile Thr Thr Val Ser Gln Glu Cys Phe Asp
85 90 95

Val Glu Asn Gly Pro Ser Pro Gly Arg Ser Pro Leu Asp Pro Gln Ala
100 105 110

Ser Ser Ser Ala Gly Leu Val Leu His Ala Thr Phe Pro Gly His Ser
115 120 125

Gln Arg Arg Glu Ser Phe Leu Tyr Arg Ser Asp Ser Asp Tyr Asp Leu
130 135 140

Ser Pro Lys Ala Met Ser Arg Asn Ser Ser Leu Pro Ser Glu Gln His
145 150 155 160

Gly Asp Asp Leu Ile Val Thr Pro Phe Ala Gln Val Leu Ala Ser Leu
165 170 175

Arg Ser Val Arg Asn Asn Phe Thr Ile Leu Thr Asn Leu His Gly Thr
180 185 190

Ser Asn Lys Arg Ser Pro Ala Ala Ser Gln Pro Pro Val Ser Arg Val
195 200 205

Asn Pro Gln Glu Glu Ser Tyr Gln Lys Leu Ala Met Glu Thr Leu Glu
210 215 220

Glu Leu Asp Trp Cys Leu Asp Gln Leu Glu Thr Ile Gln Thr Tyr Arg
225 230 235 240

Ser Val Ser Glu Met Ala Ser Asn Lys Phe Lys Arg Met Leu Asn Arg
245 250 255

Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser Gly Asn Gln Val Ser
260 265 270

Glu Tyr Ile Ser Asn Thr Phe Leu Asp Lys Gln Asn Asp Val Glu Ile
275 280 285

Pro Ser Pro Thr Gln Lys Asp Arg Glu Lys Lys Lys Lys Gln Gln Leu
290 295 300

Met Thr Gln Ile Ser Gly Val Lys Lys Leu Met His Ser Ser Ser Leu
305 310 315 320

Asn Asn Thr Ser Ile Ser Arg Phe Gly Val Asn Thr Glu Asn Glu Asp
325 330 335

His Leu Ala Lys Glu Leu Glu Asp Leu Asn Lys Trp Gly Leu Asn Ile
340 345 350

Phe Asn Val Ala Gly Tyr Ser His Asn Arg Pro Leu Thr Cys Ile Met
355 360 365

Tyr Ala Ile Phe Gln Glu Arg Asp Leu Leu Lys Thr Phe Arg Ile Ser
370 375 380

Ser Asp Thr Phe Ile Thr Tyr Met Met Thr Leu Glu Asp His Tyr His
385 390 395 400

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Ser Asp Val Ala Tyr His Asn Ser Leu His Ala Ala Asp Val Ala Gln
                405                 410                 415

Ser Thr His Val Leu Leu Ser Thr Pro Ala Leu Asp Ala Val Phe Thr
            420                 425                 430

Asp Leu Glu Ile Leu Ala Ala Ile Phe Ala Ala Ala Ile His Asp Val
        435                 440                 445

Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr Asn Ser Glu
    450                 455                 460

Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu Asn His His Leu
465                 470                 475                 480

Ala Val Gly Phe Lys Leu Leu Gln Glu Glu His Cys Asp Ile Phe Met
                485                 490                 495

Asn Leu Thr Lys Lys Gln Arg Gln Thr Leu Arg Lys Met Val Ile Asp
            500                 505                 510

Met Val Leu Ala Thr Asp Met Ser Lys His Met Ser Leu Leu Ala Asp
        515                 520                 525

Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser Ser Gly Val Leu
    530                 535                 540

Leu Leu Asp Asn Tyr Thr Asp Arg Ile Gln Val Leu Arg Asn Met Val
545                 550                 555                 560

His Cys Ala Asp Leu Ser Asn Pro Thr Lys Ser Leu Glu Leu Tyr Arg
                565                 570                 575

Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe Gln Gln Gly Asp Lys
            580                 585                 590

Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys Asp Lys His Thr
        595                 600                 605

Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr Ile Val His
    610                 615                 620

Pro Leu Trp Glu Thr Trp Ala Asp Leu Val Gln Pro Asp Ala Gln Asp
625                 630                 635                 640

Ile Leu Asp Thr Leu Glu Asp Asn Arg Asn Trp Tyr Gln Ser Met Ile
                645                 650                 655

Pro Gln Ser Pro Ser Pro Pro Leu Asp Glu Gln Asn Arg Asp Cys Gln
            660                 665                 670

Gly Leu Met Glu Lys Phe Gln Phe Glu Leu Thr Leu Asp Glu Glu Asp
        675                 680                 685

Ser Glu Gly Pro Glu Lys Glu Gly Glu Gly His Ser Tyr Phe Ser Ser
    690                 695                 700

Thr Lys Thr Leu Cys Val Ile Asp Pro Glu Asn Arg Asp Ser Leu Gly
705                 710                 715                 720
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Glu Thr Asp Ile Asp Ile Ala Thr Glu Asp Lys Ser Pro Val Asp Thr
725 730 735

<210> 8
<211> 564
<212> PRT
<213> Rattus norvegicus

<400> 8

Met Lys Glu Gln Gly Gly Thr Val Ser Gly Ala Gly Ser Ser Arg Gly
1 5 10 15

Gly Gly Asp Ser Ala Met Ala Ser Leu Gln Pro Leu Gln Pro Asn Tyr
20 25 30

Leu Ser Val Cys Leu Phe Ala Glu Glu Ser Tyr Gln Lys Leu Ala Met
35 40 45

Glu Thr Leu Glu Glu Leu Asp Trp Cys Leu Asp Gln Leu Glu Thr Ile
50 55 60

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/34045

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :C12N 9/16, 9/22, 1/20, 15/00, 5/00; C07H 21/04
US CL :435/196, 199, 252.3, 320.1, 325; 536/23.2
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/196, 199, 252.3, 320.1, 325; 536/23.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MONACO, L. et al. Structure of Two Rat Genes Coding for Closely Related Rolipram-sensitive cAMP Phosphodiesterases. MULTIPLE mRNA VARIANTS ORIGINATE FROM ALTERNATE SPLICING AND MULTIPLE START SITES. J. Biol. Chem. 07 January 1994, Vol. 269, No. 1, pages 347-357, see the entire document, especially Fig. 2 to Fig. 5.	1-18
Y	HUSTON, E. et al. Molecular cloning and transient expression in COS7 cells of a novel human PDE4B cAMP-specific phosphodiesterase, HSPDE4B3. Biochem. J. 1997, Vol. 328, pages 549-558, see the entire document.	1-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 MARCH 2001	06 APR 2001

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Dorothea Lawrence For TEKCHAND SAIDHA
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/34045

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

West search, stn search in files medline, caplus, embase, biosis, biotechds and others. Search terms used : human or mammalian phosphodiesterase, and gene or dna or rna or nucleic acid? and others. Issued US patent, EST, genebank and protein data bases search for the claimed SEQ ID NOS.